REMARKS/ARGUMENTS

Claims 66-72 and 78-90 are pending. Claims 1-65, 73-77, 84 and 86 have been canceled without prejudice. Claims 66, 67, 68, 69, 79, 82, 87 and 90 have been amended. Support for the amendments is found throughout the specification and are depicted in the drawings. Reconsideration of the rejection is respectfully requested.

Claims 67-72 and 78-90 were rejected under 35 USC 112, first paragraph as not complying with the written description requirement by containing "new matter". The language "mismatch recognizing and mismatch directed endonuclease. The examiner contends that the term "mismatch recognizing" is not supported. This rejection is respectfully traversed.

In order for an enzyme to nick or cleave at a mismatch, the mismatch must be somehow found and therefore "recognized". Furthermore, the specification discusses the enzyme's mismatch recognition and cleavage abilities on page 42, lines 5-14. Still further, the examiner considers "mismatch directed" to be supported. In order to be "directed" towards a mismatch, the mismatch must be initially (or simultaneously) recognized. All of these terms are indicating essentially the same feature, namely that the events occur at the mismatch site, not many base pairs upstream or down stream as used in the prior art. Nonetheless, the language has been amended to expedite prosecution.

Claims 67, 69-73 and 84-90 were rejected under 35 USC 102(e), as being anticipated by Vind. Vind is cited to prepare a heteroduplex and adding a cell extract, which is alleged to contain the recited activities, followed by recovering variant homoduplexes. This rejection is respectfully traversed.

This rejection is based on the assumption that the cell extract containing a DNA repair system has the claimed enzyme activities. The cell extract does not match the claims that recite a defined composition, not an undefined extract. The claims recite the presence of a single enzyme having "mismatch directed endonuclease that cleaves at the mismatched nucleotides." Vind does not mention having such an enzyme in his extract. The actual enzymes used by applicants (CEL I and others) are all plant enzymes involved in certain aspects of plant metabolism unrelated to DNA repair. CEL I is from celery and is believed

to be involved with redistribution of nutrients, perhaps for seed production. Since such enzymes are generally not part of DNA repair systems, it is unlikely for Vind to have any enzyme similar to that claimed in a bacteria DNA repair system.

The examiner has presented stretched interpretations for Vind and the claims, which regardless of its merits, does not apply to the present claims.

The examiner has contended that claim 67 may be interpreted so that the Vind Mut repair system etc. forms the multiple "agents" which perform these functions. This interpretation is not possible with the present claims, which recite a defined composition including "a mismatch recognizing and mismatch directed endonuclease that cleaves at the mismatch nucleotides". An undefined combination of agents in Vind cannot be interpreted as a defined single enzyme, even if Vind's combination operated in the same manner.

Furthermore, nothing in Vind teaches "cleaving at the mismatched nucleotides". While the repair system cleaves somewhere and large sections of DNA are replaced during the repair process, the cleavage is somewhere upstream or downstream a way, there is no indication that the cleavage occurs at the mismatch site. Therefore this first interpretation of Vind is not appropriate for the present claims.

Still further, claim 67 recites using an enzyme composition that "consists essentially of" those being used in the present invention. Normal bacterial DNA repair uses a large number of enzymes and other components and thus would not fall within the meaning of the present in vitro system. The examiner has argued that cell extracts are or render obvious an in vitro system. However, one cannot consider a cell extract to be a "defined composition" as recited in step b of either claim 66 or 67. Also, a cell extract is not a composition "wherein the enzymes consist essentially of..." but a complex mixture. Accordingly, the rejection should be withdrawn.

As a separate issue, Claim 71 depends on claim 69 and recites that the enzymes are added sequentially. This cannot be performed by Vind who uses a cell extract. Since Vind does not separate the enzymes from each other, he cannot add them sequentially.

Claim 68 was rejected under 35 USC 103 as being unpatentable over Vind. In addition to the reasons given above, the examiner contends that the particular order or any order of adding ingredients is obvious. This rejection is respectfully traversed.

All of the arguments presented above apply for this claim as well. Please note that Vind uses a cell extract. Since the enzymes are not separated from each other, they cannot be added sequentially. Even if one adds the extract multiple times, the same enzymes in the same proportion are being added each time, which does not match the claim recitations. It is not possible to separately add the enzymes in Vind. Therefore, it is contrary to the specific teachings of Vind to add any enzyme component separately because use of a cell extract is taught.

The examiner has argued that applicants have not shown anything unobvious about the order of addition. However, the reference is such that any order of addition is possible because all of the components are added at once as a cell extract. Applicants contend that a method that is impossible with the components in the reference is unobvious to perform.

Also, while the order of addition may not matter for certain reactions, as explained in previous responses, the order of addition matters for the present invention. Accordingly, this rejection should be withdrawn.

Claims 75-77 and 80 were rejected under 35 USC 103(a) as being unpatentable over Vind in view of Arnold et al. Claims 75-77 have been canceled. As for claim 80, Arnold et al is cited to show E. coli DNA repair extracts contain Pol 1. The Examiner concludes it obvious to have this present. This rejection is respectfully traversed.

Vind is concerned with using extracts with thermostable mismatch repair proteins. During the Vind process, the enzymes are subjected to high temperatures that denature DNA. E. coli enzymes are readily heat denatured and generally not considered thermostable. Therefore, one would not be motivated to use E. coli Pol 1 in the Vind method.

The examiner has argued that such a teaching away does not detract from the broader disclosure. While true in principle, review of Vind indicates the use of high temperatures is not merely a minor embodiment. The whole invention of Vind is to use thermostable enzymes, which permit higher temperatures during thermocycling as the improvement over

the prior art (e.g. the Stemmer patent family). The high temperature aspect is Vind's entire invention. Therefore, one cannot remove such an aspect from the Vind teaching and ignore the arguments above.

As a separate argument, the examiner contends that Vind uses enzymes from different species and cites the human enzyme GTBP/p160 (MSH6) as an example. However, this is not what Vind teaches. Vind merely teaches using the bacterial homolog to GTBP and the bacterial homolog to MSH6. Furthermore, the list of enzymes, which include the MSH6 homolog and the GTBP homolog, are taught to be thermostable, and even claimed as such in claim 10. It is clear that the human version of the enzyme(s) are not intended for use in the Vind method and technically the human versions are not even mentioned.

Furthermore, as presented above, one would still not have the claimed invention for the reasons given regarding Vind. Accordingly, the rejection should be withdrawn.

Claims 78, 79 and 83 were rejected under 35 USC 103(a) as being unpatentable over Vind in view of Birkenkamp et al. The examiner considers it obvious to use the Birkenkamp et al T4 mismatch correction system in the repair system of Vind. This rejection is respectfully traversed.

The two methods in the two references are producing different types of products. Vind wishes to generate a library of new polynucleotides and Birkenkamp et al wish to correct a mismatch to one of the two parent strands. The goal for one is to produce many similar polynucleotides while the goal for the other is to produce the two original parent strands. It is unclear why one would want to combine the two techniques absent the use of "hindsight".

The current claims depend on claim 67, step c, which recites producing sequence variants and increasing diversity in the population of polynucleotides. This is quite different from what the enzymes are doing in Birkenkamp et al and therefore one lacks motivation to use such enzymes.

The current claims also recite "separating and recovering at least one sequence variant" in step d. Birkenkamp et al does not want and is not motivated to separate and

recover any variant. Thus, Birkenkamp et al is not applicable to the present claims or usable in a method that does so.

Furthermore, Vind requires thermostable enzymes in their process as mentioned above. The Birkenkamp et al T4 enzymes are not sufficiently thermostable and thus it is not obvious to add something expected to be inactivated and be made useless in the process.

Still further, the Vind DNA repair system (cell extract) by itself has the polymerase, exonuclease and ligase activities. Thus, there is no purpose to adding the enzymes from Birkenkamp et al other than by use of "hindsight". Accordingly, this rejection should be withdrawn.

Claims 66-74, 81, 82 and 84-90 were rejected under 35 USC 103(a) as unpatentable over Vind in view of Oleykowski et al. In addition to the teachings mentioned above, the examiner urges Oleykowski et al teaches CEL I and that CEL I is superior to T4 endonuclease VII for mutation detection assays. The examiner concludes it obvious to use CEL I in the mismatch repair method of Vind. This rejection is respectfully traversed.

Vind is not performing a mutation detection assay. Vind does not use T4 endonuclease VII. Therefore both the use and advantage of CEL I taught by Oleykowski et al are meaningless to Vind. Furthermore, the Vind method using an extract is not deficient in any component for performing the Vind method; thus, there is no motivation to add additional components, especially those for performing a different type of method.

As claimed in claim 66, step C, the method produces sequence variants and increases the diversity in a population of polynucleotides. By contrast CEL I is taught to cleave for analysis, not produce variants or anything new at all.

Steps c and d of the present claims recite producing sequence variants and increasing diversity in the population of polynucleotides and separating and recovering the variants. Oleykowski et al does not want and is not motivated to produce, separate and recover any variant or increase diversity. Thus, Oleykowski et al is not applicable to the present claims or usable in a method that does so.

Furthermore, there is no reason for adding an enzyme such as CEL I to Vind because CEL I is not taught to be a part of any DNA repair system, much less that used by Vind. CEL I is from a celery plant whereas Vind uses bacteria. What makes the examiner think that a plant enzyme would function in cooperation with the bacterial DNA repair system? Further complicating matters, the Vind process uses thermostable enzymes to perform a method in high temperatures. There is no reason to believe that an enzyme from celery would be thermostable. The Vind Example uses 94° C, a temperature well known to be more than enough to cook celery, hardly appropriate for retaining enzymatic activity. Accordingly, this rejection should be withdrawn.

In view of the amendments and comments above, the rejections have been overcome. Reconsideration, withdrawal of the rejections and early indication of allowance are respectfully requested. If any issues remain, the examiner is encouraged to call the undersigned for prompt resolution.

If needed, applicants petition for an extension of time under the provisions of 37 CFR 1.136(a) for sufficient time to accept this response. The commissioner hereby is authorized to charge payment of any fees under 37 CFR § 1.17, which may become due in connection with the instant application or credit any overpayment to Deposit Account No.500933.

Respectfully submitted,

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Enclosure: Petition for a One-Month Extension of Time

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